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AZATADINE MALEATE IN PERENNIAL ALLERGIC RHINITIS: EFFECTS ON CLINICAL SYMPTOMS AND CHOICE REACTION TIME

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1 The efficacy of the antihistamine azatadine maleate at maximum recommended dosage (4 mg/day) for 1 week was assessed relative to placebo in a double-blind crossover study of twenty patients with perennial allergic rhinitis.

2 Sixteen patients reported significant improvement in their clinical symptoms while taking the active drug.

3 The size of skin test weals for both histamine provocation and common inhalant allergens (prick test) diminished significantly after the azatadine treatment. There was no correlation between inhibition of skin reactions and symptom improvement.

4 Eight subjects reported sedative effects attributable to azatadine maleate. Their performance on a choice reaction time task was depressed significantly after taking the antihistamine; no change relative to placebo occurred in the non-sedated group.

Introduction

Antihistamines are frequently prescribed for patients with allergic rhinitis. The drugs are generally effective particularly in seasonal allergic rhinitis, but their efficacy varies greatly between individuals and they may produce undesirable side effects, sedation being the most common. Considering the common use of antihistamine drugs and their ready availability to the general public, relatively few objective studies on the effects of these drugs on psychomotor performance have been undertaken (Molson, Mackey, Smart & Turner, 1966; Bye, Dewsbury & Peck, 1974). And many of the investigations that have been done have involved acute administration rather than chronic administration, although the latter is the normal practice for antihistamine therapy.

Introduction of another effective antihistamine broadens the therapeutic selection in a field where, as well as providing symptom relief, therapy must be suited to individual tolerance. Azatadine maleate (Zadine® Schering Corporation USA) is a relatively new antihistamine with both anticholinergic and anti-serotonin activity which is reported to have prolonged action with considerable increase in potency over cyproheptadine and chlorpheniramine in protecting sensitised guinea pigs against histamine challenge (Tozzi, Roth & Tabachnick, 1974). In humans it is reported to have minimal sedative effects resulting from its low therapeutic dose requirements (manufacturer's professional brochure), and to be effective in the treatment of allergic and vasomotor rhinitis and urticaria (Tozzi *et al.*, 1974). Few clinical data were available in the literature published in English.

The present study was undertaken to assess the clinical effects of azatadine in patients with perennial allergic rhinitis and to determine by means of objective and self-report measures, the occurrence of any adverse reactions when it was administered at the maximum recommended therapeutic dose of 2 mg two times a day over a period of 7days.

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Methods

Subjects

Twenty patients (13 women and 7 men) ranging in age from 15 to 55 years (mean age 26) participated in the trial. All presented with perennial allergic rhinitis manifested by one or more of the following symptoms; rhinorrhoea, conjunctivitis, sneezing, blocked nose and nasal pruritis. Fourteen patients experienced symptoms which varied little in severity throughout the year, five patients had perennial rhinitis with considerable seasonal exacerbation, and one patient had mild perennial rhinitis with severe allergic conjunctivitis as the major presenting symptom. No patients had any other serious illness or required other medication (oral contraceptives excepted) for 2 weeks prior to or during the study.

Approval for the clinical trial was obtained from the Standing Committee on Therapeutic Trials of the New Zealand Department of Health. Informed consent was obtained from the twenty subjects.

Design and procedure

This was a double-blind, placebo controlled, cross-over study in which each patient served as his own control. Eleven patients received placebo (2 tablets twice daily) for 7 days followed by azatadine (2 mg twice daily) for 7 days. Nine patients took the same regime in reverse order. Treatment order was allocated randomly, the subjects avoided alcohol, and were cautioned against driving for the duration of the trial. The patients were assessed on clinical and laboratory criteria before beginning the trial, and after each drug course between 1 and 2 h after taking the final dose, when peak therapeutic levels would be expected (Pearlman, 1976).

Atmospheric pollen and spore concentrations were monitored throughout the trial period. No changes that would be expected to influence the results of the study were noted.

Clinical assessment

All patients were examined to exclude those with nasal obstruction due to septal deformations or polyps, and those patients where bacterial infection might provide the major explanation for their symptoms. A careful history was recorded and the severity of each symptom was graded on a scale of 0-3 where 0 = nil, 1 = mild, 2 = moderate, and 3 = severe. After each course of treatment, the patients were asked to assess their symptoms on this scale and then to describe any reactions they attributed to taking the tablets. Then they were questioned systematically about the incidence of specific side effects typical of antihistamine drugs; sedation, disturbance in powers of concentration, feelings of weakness, nausea, abdominal pain, headache, visual disturbance, mood changes, dryness of the mouth and increased appetite. These results were also recorded on a scale of 0 to 3.

Allergic status

Each patient was tested for immediate hypersensitivity to twelve common inhalant allergens by the modified skin prick test (Pepys & Davies, 1978), performed on the anterior surface of the forearm. Allergen extracts were supplied by Hollister-Stier Laboratories, Spokane, Washington, U.S.A. The diameters of the weals produced in positive tests were measured with a plastic ruler and recorded in mm. At least two of the skin tests positive at the initial visit were repeated after both the placebo and active drug courses. Eighteen of the twenty patients had one or more positive skin reactions to inhalant allergens. The other two had clearly defined food allergies.

Histamine provocation in the form of prick test with 1% histamine acid phosphate was performed during each visit. Serum IgE levels were measured for each patient at the initial visit using the Prist assay (Phadebas, Pharmacia). IgE concentration was higher than 100 IU/ml in 11 of the twenty patients.

Choice reaction time tasks are frequently used to assess sedative drug effects in man (e.g. Hindmarch & Parrott, 1978; Ideström, 1960; Ideström, Schalling, Carlquist & Sjöquist, 1972), and have been utilised in various forms to evaluate antihistamines. Biehl (1979) found that performance in a complex reaction time test involving both hand and foot movements was significantly impaired by acute administration of 8 mg of azatadine maleate. Hindmarch & Parrott (1978), and Kulshrestha, Gupta, Turner & Wadsworth (1978) observed no impairment of performance in complex reaction time tasks after therapeutic doses of several different antihistamines.

The Choice Reaction Time (CRT) task employed for this study utilized a horizontal row of eight lights, a corresponding group of eight response buttons, a 'starting key', and a warning light which was positioned centrally. The warning light preceded each trial by an average of 7.5 s (range 5 to 10 s) and served to ready the subject for the forthcoming trial. The subject's task was then to observe the array of eight signal lights and to depress the corresponding switch as quickly as possible when one of the lights was illuminated. Stimulus lights were activated in a random sequence. Each light position was tested in random sequence three times for a total of 24 trials, which encompassed about 7.2 min testing time. Any errors (failure to press the correct response button) were automatically recorded and these trials were repeated at the end of the task. The CRT was controlled by a PDP 8 computer, thereby ensuring

standardized presentation of stimuli and precise collection of results.

Two components of reaction time were derived separately. Lift time referred to the interval between onset of the signal light and release of the starting key. Jump time referred to the interval between release of the starting key and depression of the appropriate response button. Total reaction time was a composite of the above two measures. Additionally the variability (expressed as the coefficient of variation) of lift and jump times was computed.

Each subject completed the CRT task twice during each visit. Only the results of the second test were analysed, the first being treated as a warm-up task.

Results

Sixteen of the twenty patients experienced substantial relief of their symptoms while taking azatadine. Two patients improved on and preferred the placebo and two patients reported minimal symptoms over the trial period and were unable to make an effective comparison between the two treatments. The mean symptom scores after azatadine and placebo are recorded in Table 1. These show that for each

Table 1 Mean symptom scores

Symptom	*Placebo*	*Azatadine*	*Number of patients with this symptom improved with azatadine*
Rhinorrhoea	1.35	0.725	10
Conjunctivitis	0.83	0.3	10
Sneezing	1.125	0.325	11
Nasal blockage	1.15	0.425	8
Nasal pruritis	0.525	0.4	5
Total	4.98	2.175	

of the symptoms assessed, the mean score was less for azatadine than for placebo with the total mean symptom score declining from 4.98 on placebo to 2.17 on azatadine. Statistically this improvement was highly significant as determined by the Wilcoxon matched pairs test ($P < 0.01$) (Siegel, 1956). Sneezing, rhinorrhoea and nasal blockage were the symptoms which improved most. Nasal pruritis was little affected. The patient with severe conjunctivitis associated with mild rhinitis had almost complete relief from his symptoms with the active drug. The average skin reactions to 1% histamine declined on average from 4.1 mm after placebo to 2.5 mm after azatadine. The result was statistically highly significant as assessed by a *t*-test for matched pairs ($t = 6.02$, $P < 0.001$).

Positive skin weals to allergens were obtained in eighteen subjects and in most instances the patients were allergic to two or more inhalants. In these instances the mean weal size was calculated for each individual on each drug course. The mean size of the positive weals from allergens was 6.21 mm after placebo, declining to 3.31 mm after azatadine, a difference which was significant as determined by the Sign test ($P < 0.02$, Siegel, 1956). Despite these substantial reductions in mean weal size on the active drug there were six patients whose skin reactions to histamine declined by one millimetre or less on azatadine, and four patients with skin reactions to allergens which exhibited no change in weal size after the active drug or placebo. There was no correlation between improvement in symptoms and extent of inhibition of either histamine- or allergen-induced weal.

Side effects

A number of patients experienced side effects typical of antihistamines with either azatadine or placebo or both (Table 2). The most common side effect was sedation which occurred in eight subjects (six women and two men) taking azatadine and two taking placebo. All but two of these found that their power of concentration was impaired in the sedated state, and most felt 'irritable'. With the exception of one report of dry mouth only, all the incidences of other side effects were reported concurrently with sedation. Because of severe sedative effects two patients terminated their azatadine courses after 5 of the planned 7 days; in these cases the appropriate tests were performed on the fifth day of therapy. Headache occurred with the same frequency with azatadine and placebo. Three patients experienced blurred vision while taking the active drug. Three patients spontaneoulsy reported having 'dry mouth' after taking azatadine, and three reported this after specific questioning following the placebo course.

All patients who reported side effects experienced symptom relief.

Table 2 Number of patients reporting side effects after each drug course

Side effect	*Placebo*	*Azatadine*
Sedation	2 (1)	8 (6)
Concentration impaired	2 (1)	6 (3)
Weakness	1	3
Nausea	1	3 (1)
Abdominal pain	0	1
Headache	4 (1)	4 (1)
Visual disturbance	0	3 (2)
Mood	2	6 (1)
Dry mouth	3	4 (3)
Increased appetite	0	1 (1)

Figures in parentheses = number of patients who reported side effect 'spontaneously'.

Choice reaction time task

Subjects were assigned to two groups (sedated *v* non-sedated) on the basis of whether sedative effects were reported whilst taking azatadine. The respective means for the sedated, the non-sedated and the combined groups are presented in Table 3. There was a tendency for those subjects reporting sedation on azatadine to respond more slowly during the choice reaction time task, whereas the remaining subjects showed no evidence of slowing.

Table 3 Means presented by group and drug condition

	Placebo	*Azatadine*
Lift time (ms)		
Sedated	397	450
Non-sedated	457	446
Combined totals	433	448
Jump time (ms)		
Sedated	370	445
Non-sedated	400	390
Combined totals	388	412
Total reaction time (ms)		
Sedated	767	911
Non-sedated	836	817
Combined totals	821	860

The data were analysed using a 3-factor analysis of variance (ANOVA) (Winer, 1971) in which the effects of drug order, group (sedated *v* non-sedated) and drug (placebo *v* azatadine) were examined. Without exception the drug order factor was non-significant indicating that there were no effects due to drug sequence. The ANOVA summaries for group, drug and their interactions are presented in Table 4.

Lift time did not differ between the two groups or as a function of drug condition. There was no statistical confirmation of differential slowing in the sedated group although performance appeared to deteriorate somewhat on the active drug (Table 3).

For jump time, the sedated group showed significantly more slowing than the non-sedated group on azatadine ($P < 0.05$). However, there was no overall effect of drug in the *combined* groups on this variable. Similar findings were obtained for total reaction time. The sedated group again showed a performance deficit on the drug relative to the non-sedated group whose performance remained essentially unchanged. The main effect of azatadine on performance of the combined groups was non-significant ($P < 0.10$) (Table 4).

Individual variability was also analysed for each of the response measures but as none of these comparisons approached statistical significance the results do not warrant presentation.

Table 4 ANOVA summary for reaction time data

	Mean squares	*F*	*Probability*
Lift time			
Between subjects			
Group	0.0030	0.24	—
Residual	0.0128	—	—
Within subjects			
Drug	0.0945	0.98	—
Group × drug	0.0089	1.97	.18
Residual	0.0045	—	
Jump time			
Between subjects			
Group	0.0044	0.08	—
Residual	0.0548	—	
Within subjects			
Drug	0.0198	2.59	.12
Group × drug	0.0176	4.61	.05
Residual	0.0038	—	
Total reaction time			
Between subjects			
Group	0.0014	0.01	—
Residual	0.0952	—	
Within subjects			
Drug	0.0966	2.92	.10
Group × drug	0.0631	5.04	.04
Residual	0.0125	—	

Degrees of freedom were 1 and 16 througout. All other interaction terms were non-significant.

Discussion

Antihistamines are generally regarded as being more effective in controlling the symptoms of seasonal allergic rhinitis than those of perennial rhinitis (Avery, 1976). Azatadine maleate is described as being effective in treatment of acute and chronic allergic rhinitis, vasomotor rhinitis, urticaria, and certain atopic and contact dermatitis (manufacturer's professional brochure; Tozzi *et al.*, 1974). At the maximum recommended therapeutic dose of 4 mg per day, azatadine taken over a course of 7 days significantly reduced the severity of the perennial allergic rhinitis in the majority of our patients. The sizes of the weals resulting from the histamine provocation and allergen skin tests were significantly reduced. Most patients reported that these were less itchy than weals produced by the same test before the trial and after the placebo course. However, some patients who showed little or no reduction in size of weal with the active drug experienced considerable relief of symptoms while taking the drug.

At the maximum recommended dosage azatadine maleate produced varying degrees of sedation in eight of the twenty subjects. These results conflict with those of Biehl (1979) who found no impairment of psychomotor function at this dosage. However, Biehl's studies (1979) included only normal healthy men whereas ours had a majority of women and

therefore the difference may well be dose related due to the expected differences in body weights of the two groups. Six of the eight patients reporting sedation were in fact women, and with one exception all other side effects occurred in the sedated group, all of whom experienced considerable symptom relief. Several reported that their drowsiness diminished after the first 2 or 3 days of drug treatment, while symptom control was maintained. This decrease in central nervous system depression has been discussed elsewhere (Melville, 1973; Bye, Claridge, Peck & Plowman, 1975). Eight of the twelve trial participants who had no side effects experienced good symptom control.

An important feature of this study related to the objective measurement of sedation. Although sedation is a common side effect of antihistamine drugs, the objective measurement of central nervous system depression in subjects taking these drugs is difficult (Hindmarch, 1976; Hughes & Forney, 1964). Most normal individuals can compensate for minor disturbance in alertness and motor function while performing standard psychomotor tasks of limited duration. However, the results of the choice reaction time task used in this study correlated very accurately with the subjective reports of sedation and demonstrated that the eight patients who reported sedation after maximal dosage of azatadine maleate did experience deterioration in jump time and total reaction time. This suggests that the choice reaction time task may be of considerable clinical usefulness in the future assessment of sedative reactions in antihistamine treatment.

At the maximum recommended dosage of 4 mg per day azatadine maleate was effective in controlling the symptoms of perennial allergic rhinits in 80% of cases and was generally well tolerated. Sedation was reported by 40% of our patients but tended to diminish over the 7 day course. The results of the choice reaction time task utilised here demonstrate that this type of test is well suited to studies where measurement of central nervous system depression in normal subjects on antihistamine therapy is required.

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